Remarks/Arguments

The foregoing amendments to the claims are of formal nature, and do not add new matter. Claims 119-124 are pending in this application and are rejected on various grounds. Claim 124 has been canceled without prejudice or disclaimer. Claim 119 has been amended for clarity. The rejections to the presently pending claims are respectfully traversed.

Specification

The disclosure was objected to by the Examiner as containing "embedded hyperlink and/or other form of browser-executable code." The foregoing amendment to the specification which deleted all embedded hyperlinks, is believed to overcome the present objections.

In addition, amendments to the specification have incorporated the requisite assurances that "all restrictions imposed by the depositor on the availability to the public of the deposited material will be irrevocably removed upon the granting of the pertinent U.S. patent."

Regarding the comment that pages 303-306 of the specification are missing, Applicants enclose a copy of the stamped return postcard received from the USPTO. This is *prima facie* evidence that all pages, including pages 303-306, were present at the time of filing of this application. For the Examiner's reference and convenience, Applicants have also attached copies of pages 303-306 with this response.

Accordingly, Applicants believe that the objections to the specification should be withdrawn.

Claim Rejections – 35 USC § 101 and 112, first paragraph

Claims 119-124 are rejected under 35 U.S.C. §101 allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility." Claims 119-124 are also rejected under 35 U.S.C. §112, first paragraph allegedly "since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility, one skilled in the art would not know how to use the claimed invention".

The Examiner specifically noted that "the utilities that pertain solely to nucleic acids would not convey to the encoded protein or antibody that binds it" and therefore concludes that no asserted utility is specific for PRO341 protein. The Examiner also asserts that she is unable to find either in the specification or in the art, an explanation of how Ct values are calculated, nor

what the significance of such are. Thus the Examiner concludes that the data does not support an implicit conclusion that PRO341 shows a positive correlation with lung cancer, or that it is diagnostic for such. Further, the Examiner also alleges that since the data are not corrected for aneuploidy, and because it does not necessarily follow that an increase in gene copy number results in increased gene expression, the data does not support that PRO341 or its antibody can be used as a cancer diagnostic.

Applicants respectfully disagree with and traverse the rejection.

Applicants submit that they rely on the gene amplification assay for patentable utility which was first disclosed in U.S. Provisional Application 60/092182, filed July 9, 1998, priority to which has been claimed in this application. Hence, the effective filing date of the present application is **July 9, 1998.**

Gene amplification is an essential mechanism for oncogene activation. The gene amplification assay is well-described in Example 170 of the present application, the inventors isolated genomic DNA from a variety of primary cancers and cancer cell lines that are listed in Table 9 (pages 539 onwards of the specification), including primary lung cancers of the type and stage indicated in Table 8 (page 546). As a negative control, DNA was isolated from the cells of ten normal healthy individuals, which was pooled and used as a control (page 539, lines 27-29). Gene amplification was monitored using real-time quantitative TaqMan™ PCR. The gene amplification results are set forth in Table 9A. As explained in the passage on page 539, lines 37-39, "the results of TaqMan™ PCR are reported in ΔCt units. **One unit** corresponds to one PCR cycle or approximately a **2-fold amplification**, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). PRO341 showed approximately 1.12-1.33 ΔCt units which corresponds to $2^{1.12}$ -$2^{1.33}$- fold amplification or **2.173 fold to 2.514-fold** amplification in lung tumors. This disclosure in the specification should address the Examiner's concerns regarding calculation of Ct values.

Further, to address the Examiner's issues concerning the TaqMan™ assay, Applicants submit a Declaration by Dr. Audrey Goddard with this response and particularly draw the Examiner's attention to page 3 of the declaration which clearly states that:

"It is further my considered scientific opinion that an at least **2-fold increase** in gene copy

number in a tumor tissue sample relative to a normal (i.e., non-tumor) sample is significant and useful in that the detected increase in gene copy number in the tumor sample relative to the normal sample serves as a basis for using relative gene copy number as quantitated by the TaqMan PCR technique as a diagnostic marker for the presence or absence of tumor in a tissue sample of unknown pathology. Accordingly, a gene identified as being amplified at least 2-fold by the quantitative TaqMan PCR assay in a tumor sample relative to a normal sample is **useful as a marker for the diagnosis of cancer**, for monitoring cancer development and/or for measuring the efficacy of cancer therapy" (Emphasis added).

The Declaration also confirms that based upon the gene amplification results set forth in Table 9A, one of ordinary skill would find it credible that the PRO341 nucleic acid is a diagnostic marker of human lung cancer.

Regarding the Examiner's rejection based on a lack of accounting for aneuploidy, Applicants have enclosed a Declaration by Dr. Avi Ashkenazi, Ph.D., an expert in the field of cancer biology and an inventor of the present application. As Dr. Ashkenazi explains,

> An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, gene amplification of a gene, whether by aneuploidy or any other mechanism, is still useful as a diagnostic marker.

Regarding the Examiner's point that "no asserted utility is specific for PRO341 protein and antibodies," Applicants submit, as discussed below, that the Examiner has not established a *prima facie* case for lack of utility and also discuss the utility of the PRO341 polypeptide and antibodies.

Evidentiary Standard

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the

art to question the objective truth of the statement of utility or its scope." *In re* Langer, 503 F.2d 1380,1391, 183 USPQ 288, 297 (CCPA 1974). See, also *In re* Jolles, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re* Irons, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977).

Compliance with 35 U.S.C. § 101 is a question of fact. Raytheon v. Roper, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. In re Oetiker, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992) Thus, to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner made a proper *prima facie* showing of lack of utility, shifts the burden of rebuttal to the applicant. The issue will then be decided on the totality of evidence.

A prima facie case of lack of utility has not been established

The Examiner bases the conclusion of lack of utility/ enablement on a quote from Pennica *et al.* According to the quoted statement, "WISP-1 gene amplification and expression in human colon tumors showed a correlation between DNA amplification and over-expression, whereas overexpression of WISP-3 RNA was seen in the absence of DNA amplification. In contrast, WISP-2 DNA was amplified in colon tumors, but its mRNA expression was significantly reduced in the majority of tumors compared with expression in normal colonic mucosa from the same patient". From this, the Examiner correctly concludes that increased copy number does not *necessarily* result in increased protein expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist. The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation.

Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level.

Even if a prima facie case of lack of utility had been established, it should be withdrawn on consideration of the totality of evidence

Even if one assumes arguendo that it is more likely than not that there is no correlation between gene amplification and increased mRNA/protein expression, a polypeptide encoded by a gene that is amplified in cancer would still have a specific and substantial utility. Applicants once again rely on the Dr. Avi Ashkenazi's declaration which explains that,

> "even when amplification of a cancer marker gene does not result in significant over-expression of the corresponding gene product, this very absence of gene product over-expression still provides significant information for cancer diagnosis and treatment. Thus, if over-expression of the gene product does not parallel gene amplification in certain tumor types but does so in others, then parallel monitoring of gene amplification and gene product over-expression enables more accurate tumor classification and hence better determination of suitable therapy. In addition, absence of over-expression is crucial information for the practicing clinician. If a gene is amplified but the corresponding gene product is not over-expressed, the clinician accordingly will decide not to treat a patient with agents that target that gene product".

Thus, Applicants have demonstrated utility for the PRO341 polypeptide and for the antibody that specifically binds to PRO341, for example, in detecting over-expression or absence of expression of PRO341. Further, based on this utility and the disclosure in the specification, one skilled in the art would know how to use the claimed polypeptides at the time of filing.

Hence, these data clearly support a role of PRO341 as a lung tumor marker. Accordingly, the present 35 U.S.C. §101 utility and 35 U.S.C. §112, first paragraph rejections should be withdrawn.

Claim Rejections – 35 USC § 112, second paragraph

Claims 119-124 were rejected under 35 U.S.C. §112, second paragraph for being indefinite. The Examiner alleges that "neither the claims, the specification, not the art make clear what the difference between "bind" and "specifically binds" is ... one of ordinary skill in the art

would not be reasonably apprised of the scope of the invention". Applicants respectfully traverse this rejection.

Without acquiescing to the propriety of this rejection and solely in the interest of expedited prosecution in this case, Applicants have canceled claim 124 and have amended claim 119 to recite "specifically binds". Applicants submit that the art-recognized meaning of "specific" binding is that the antibody that specifically binds to a particular antigen does not significantly cross-react with another antigen. Accordingly, one skilled in the art would knows what the scope of the invention is.

Accordingly, Applicants respectfully request that this rejection to claims be withdrawn.

The present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39780-2730P1C2). Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: October 24, 2003

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